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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/505,482	STREBHARDT ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *24-29 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 August 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/23/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Election/Restrictions

The Examiner thanks Applicants' for their timely election, with traverse, of Group I, Claims 1–23 and 30, in the reply filed on October 24, 2005. Applicants' further election, with traverse, of siRNA4, recited in claim 5, is also acknowledged.

With regard to the election of Group I, the traversal is on the ground(s) that unity of invention is present since the disclosure in Wolf et al. does not anticipate the presently claimed subject matter because the Wolf et al. reference does not enable the skilled artisan to prepare an oligonucleotide directed to PLK. Accordingly, Applicants request examination of Group III, claim 31, with the elected group.

As to the election of siRNA4, Applicants argue that the claimed siRNAs, siRNAs 2–5, recited in claim 5, share a common chemical structure in that they all contain ribose, phosphoric acid, purines, and pyrimidines, and they all share a common property in that they all inhibit the activity of PLK1 in mammalian cells.

Applicants' arguments have been fully considered but are not found persuasive for the following reasons. With regard to the election of Group I, it is agreed that Wolf does not disclose a specific antisense sequence for the PLK1 gene; however, for purposes of this restriction, according to PCT Rule 13.2, the Wolf et al. (2000) reference is used only to show that the special technical feature of Groups I and III—an agent that reduces or inhibits the activity of polo like kinase 1—is not a contribution over the prior art. Wolf et al. clearly teach that antisense

oligonucleotides directed to PLK1 were known in the art prior to the effective filing date. Accordingly, unity of invention is lacking.

With regard to the election of siRNA4, the Examiner submits that the restriction as applied to the individual siRNA sequences is proper in that the sequences do not share a significant structural element, as defined by the Administrative Instructions under PCT, Annex B(f)(i) and Annex B(f)(ii). While it is agreed that each of the alternative siRNAs comprise ribose, purines, and pyrimidines, these elements do not constitute a significant structural element in the context of the claimed invention: an siRNA that specifically inhibits the activity of polo like kinase 1. Essentially all ribonucleic acids (e.g., tRNA, rRNA, and mRNA) contain ribose, purines, and pyrimidines, but only select few inhibit PLK1 mRNA. It is the sequence as a whole, not the chemical subunits, that comprises the significant structural element of an siRNA. In the instant case, the claimed sequences are structurally distinct one from the other in that they have different nucleotide sequences and target different regions on the target mRNA. Thus, on their face, the claimed sequences do not share a significant structural element. Therefore, unity of invention is lacking.

The requirement is still deemed proper and is therefore made FINAL.

Status of the application

Claims 1–31 are pending. Claims 24–29 and 31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Amendments

Applicants' amendment to page 1 of the specification, Cross References to Related Application, adding a statement that the instant application is 35 USC §371 National Phase Entry Application from PCT/ep03/01809 is acknowledged. The amendment is entered into the application.

Specification

It is noted that the abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

Sequences

A review of the instant claims shows that this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

In the instant case, the amino acid/nucleic acid sequences set forth in Figs. 13A and 17A, Table I (page 1/1 of the specification), and in pages 59, 65, 68, 69, and 70, do not have SEQ ID NO: identifiers as currently required by 37 CFR § 1.821. Applicant is requested to amend the instant application to provide the corresponding SEQ ID NO: identifiers. Additionally, for

completeness, Applicants are advised to review the entire disclosure for compliance with 37 CFR §1.821(a)–(g).

Applicant is requested to return a copy of the attached Notice to Comply with the reply.

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Additionally, Table I is objected to because it contains non-English text, which cannot be interpreted by the Examiner. Thus, at present, Table I cannot be relied upon for support for the instant claims. The table should be amended to replace non-English text with English and to add SEQ ID NO: identifiers to the sequences listed therein.

Claim Objections

Claims 1–5 and 21-23 contain the grammatically awkward phrase "characterized in that it contains." It is suggested that the phrase be amended or replaced to more precisely claim the invention.

Claim 13 appears to contain a typo. A "b)" character appears in line 2, which does not appear to be necessary to the claim.

Claim 19 recites the phrase "is contained in an amount suitable for delivery." The phrase is grammatically awkward and unclear. How can an agent be contained in an amount suitable for delivery? What is an amount suitable for delivery. The instant application does not specify an amount suitable for delivery. The instant claim appears to be drawn to a composition, since it appears to limit claim 6 by specifying a concentration of agent suitable for delivery to a patient. Alternative phrasing might be, for example, "A composition comprising a pharmaceutically acceptable carrier and the agent of claim 6 in an amount suitable for delivery of … "

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-6, 9, 13, and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 recites a series of siRNA molecules, wherein the siRNA sequences are specified according to the complementary positions in a PLK1 target sequence. The claim is indefinite because the PLK1 sequence is not set forth in the claim or the specification. Thus, the sequences of the claimed siRNAs cannot be determined from the instant claim—i.e., there is no reference point or context for the recited "positions."

The instantly claimed siRNAs are more properly recited with the use of SEQ ID NO: identifiers. Suggested language for claiming the instant siRNAs is, for example, "An agent according to claim 4, wherein the agent is a double stranded RNA comprising a sequence selected from the group consisting of SEQ ID NO: #, #, #, and #." Applicants are advised, however, that amending the claim in this way, to overcome this rejection by reciting specific and distinct SEQ ID Nos., may render the claim subject to restriction since different siRNAs are considered to represent independent and distinct inventions that differ both structurally and functionally.

Claim 6 recites the phrase "at least one genetic information homologous to the PLK1 gene" to refer to a sequence element in an expression vector. The phrase is unclear and

somewhat confusing in that it is not clear how a "genetic information" can be homologous to a gene. Furthermore, the use of the term "information" to define a genetic sequence does not appear to be a standard usage. The term "information" is defined by The American Heritage Dictionary to be knowledge derived from study, experience, or instruction, or a collection of facts or data. It is, therefore, grammatically awkward to refer to the concept of information in the singular sense as in Claim 6. Other claims, reciting "genetic information," considered to be indefinite for the same reasons, are claims 9 and 13.

Claim 23 recites an antisense oligonucleotide referred to as "P12 and/or P13". First, if P12 and P13 are separate sequences, as they appear to be based on disclosure at page 27, Fig. 8, of the instant application, it is unclear how an antisense oligonucleotide can be both P12 and P13. No such oligo is described in the specification and it is unclear how the sequences are to be linked or combined to form a single antisense oligo. Second, if "P12" and "P13" do represent separate antisense sequences, the sequences of P12 and P13 cannot be presently examined since the sequences cannot be determined from the disclosure or the claim. Accordingly, the metes and bounds of claim 23 cannot be determined. If Applicants are seeking to claim specific antisense sequences, the sequences would be properly recited as SEQ ID NOS, and a paper copy of the raw sequence listing each sequence, and computer readable format copies of each sequence would be required for search purposes.

Claim 3 recites the limitation "the RNA" in line 1. There is insufficient antecedent basis for this limitation in the claim. The limitation is in reference to claim 2, which recites two types of RNA. Thus, it is unclear whether the limitation refers to the siRNA or antisense RNA.

Claims 4 and 5 recite the limitation "the dsRNA" in lines 2 and 1, respectively. There is insufficient antecedent basis for these limitations in the claims.

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23 and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, complete or partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

The claims are drawn generally to an agent for inhibiting development or progress of proliferative diseases, wherein the agent is one that reduces or inhibits the activity of polo-like

kinase 1 in mammalian cells. Thus, the claims are extremely broad, encompassing all possible organic and inorganic compounds, polymers, vectors, viruses, nucleic acids, and proteins having the ability to target and inhibit any form of PLK1, including any variant or isoform, from any species in mammalian cells. It is important to note that, as currently written, Claim 1 does not require that PLK1 be a mammalian PLK1; it requires only that the reduction or inhibition of PLK1 take place in mammalian cells. Accordingly, an embodiment within the scope of the invention are mammalian cells transfected with plasmids expressing any form of PLK1, or any gene expressing a polo-like kinase 1 activity. Thus, the claims encompass agents targeting any PLK1 from any species. Moreover, information provided on page 1 of the specification indicates that the polo-like kinase family is large and diverse:

> A key regulator for the mitotic progression in mammalian cells is the polo-like kinase (PLKI) which is structurally related to the polo gene product of Drosophila melanogaster, Cdcsp of Saccharomyces cerevisiae and plo1+ of Schizosaccharomyces pombe [...]. The PLKs from yeast, insects, amphibians and mammals represent a group of serine/threonine kinases that share a high degree of homology suggesting that the proteins have a close evolutionary and thereby functional relationship. (page 1)

Adequate written description does not exist in the instant application for all these agents. That is, the specification does not adequately allow persons of ordinary skill in the art to recognize that applicant(s) were in possession of the entire genus of agents as now claimed in the instant claims.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry,

whatever is now claimed (pg. 1117). Because the level of skill and knowledge in the art increases over time, it is essential to determine possession as of the effective filing date.

In the instant case, the specification does not clearly allow persons of ordinary skill in the art to recognize that Applicants invented what is now claimed. The application does not enable the skilled artisan to clearly envision the detailed chemical structures of the encompassed genus of agents that inhibit the activity of all forms of PLK1 from all possible species, and that thereby inhibit the development or progress of proliferative diseases.

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

While the specification adequately describes certain specific inhibitory RNAs such as siRNAs and antisense oligonucleotides, and adequately describes certain specific inhibitory peptides and/or antibodies directed against PLK1 (apparently human PLK1) (see pages 33-78) by fully setting forth their structures and functions, and by describing the materials and methods needed to make and use these agents, adequate written description does not exist for the virtually unlimited number of other siRNAs, antisense oligos, and peptides directed against all other PLK1s, nor does adequate written description exist for the virtually unlimited number of other inhibitors and antagonists in the claimed genus. As stated above, the claimed genus is extremely large, including virtually any organic or inorganic agent having the ability to reduce or inhibit all forms of PLK1 activity derived from any species. Applicants have not shown possession of the

entire genus. Rather applicants describe a narrow subset of agents; specifically, certain structurally defined siRNAs, antisense oligos, and peptides.

Moreover, while claims 6-19 broadly claim an RNA expression system having a "genetic information homologous to PLK1," written description is not found for the virtually unlimited number of possible sequence elements that might be used in this expression system to specifically inhibit the activity of PLK1 and, thereby, stop the progress of proliferative diseases.

MPEP §2163 states, in part: "[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)."

Accordingly, only methods comprising the use of the disclosed, sequence-specific inhibitory siRNAs, shRNAs, and peptides meet the written description requirement.

Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim1 is rejected under 35 U.S.C. 102(b) as being anticipated by Holtrich et al. (1994) *Proc. Natl. Acad. Sci.* 91:1736–1740.

Holtrich et al. show that cycloheximide, an inhibitor or protein synthesis, prevents PLK (polo-like kinase) mRNA expression in mitogen-activated human lymphocytes (pp. 1738-9, and Fig. 7). Additionally, Holtrich et al. show that bacterial lipopolysaccharide represses PLK mRNA expression in human macrophages (page 1739, Fig. 8). Accordingly, Holtrich et al. anticipate claim 1 in that they teach an agent—cycloheximide and/or bacterial lipopolysaccharide—that reduces or inhibits the activity of polo-like kinase 1 in mammalian cells.

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Claims 1–4, 20–22, and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Elez et al. (2000) *Biochemical and Biophysical Res. Comm.* 269:352–356.

Elez et al. teach a 19-mer antisense phophorothioate-modified oligonucleotide, JWG2000, that inhibits PLK1 expression in culture in human carcinoma cell lines A549 and Detroit 562, and *in vivo* in A549 xenografts in nude mice (pp. 352–355, Figs. 1, 2, and 4). The specific sequence of the exemplary antisense oligo, JWG2000, is disclosed on page 353, second column. Upon transfection into cultured cells, the oligo is shown to reduce PLK1 mRNA and

protein expression levels (Figs 1 and 2). Upon bolus delivery to nude mice, the antisense oligo is shown to have an antineoplastic effect in that tumor size is decreased. The authors state (page 354) that down-modulation of PLK1 expression with JWG2000 was accompanied with decreased proliferation and viability of cancer cells, and a decrease in tumor size in treated animals. For administration to mice, the oligonucleotide was dissolved in saline solution (page 353) to produce a pharmaceutical composition within the scope of claim 30.

Accordingly, the instant claims are anticipated by Elez et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 6–11, 13, 14, 16–18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holtrich et al. (1994); Elez et al. (2000); and Driscoll et al. (WO 01/49844 A1).

The instant claims are drawn generally to an agent that reduces or inhibits the activity of polo-kinase 1 in mammalian cells, comprising an RNA expression system having an interfering RNA coding region under transcriptional control of a promoter. Claims 7–19 further limit the invention by stating that the interfering RNA is, for example, a hairpin RNA having a spacer sequence, which may be 3-10 nts long, and intracomplementary sequences, 15-30 nucleotides long; and that the expression system is a plasmid or viral vector, which may also comprise a termination signal. The plasmid promoter may be a U6 or H1 promoter, and the expression system may be formulated (e.g., with buffered saline) for intravenous administrations, specifically bolus injections. The recitation of a nuclease inhibitor in claim 6 is not considered to be limiting for purposes of this rejection since the claim recites that the inclusion of a nuclease inhibitor is "optional." Thus, claim 14, reciting wherein the nuclease inhibitor is ATA, is, similarly, not considered to be a limitation that must be met by the references relied upon for this rejection.

Holtrich et al. (1994) teach the cDNA sequence of human polo-like kinase, deposited as GenBank accession no. X75932. Thus, the *plk* sequence is shown in the prior art. Holtrich et al. do not teach an antisense RNA, siRNA, or hairpin RNA expression construct according to claims 6–19.

Elez et al. is relied upon for the reasons given above. Elez et al. teach an antisense sequence for down regulating the *plk1* gene, thereby reducing PLK1 activity. Elez et al. further teach that Plk1 is a highly conserved mitotic serine/threonine kinase that is overexpressed in cancer cell lines and that PLK1 could serve as a suitable diagnostic and prognostic marker for tumor progression and as target for anti-cancer therapy (page 352). Moreover, interference with PLK1 expression at the mRNA level leads to loss of cell viability, blockage of tumor cell proliferation, and induction of mitotic death in Plk1-overexpressing cell lines. Thus, antisense ODNs against Plk1 mRNA may provide a novel therapeutical concept to inhibit the production of Plk1 protein via antisense-induced degradation of its mRNA. Elez et al. state that Plk1 seems an excellent target for antisense anti-tumor therapy since it plays a major role in G2/M transition and, via Cdc25C activation and cyclin B degradation in telophase, also controls the cells' exit from mitosis (page 355).

Elez et al. further teach that antisense oligodeoxynucleotides (ODNs) offer potential not only for investigation of gene expression, but also as therapeutic agents by altering the intermediary metabolism of RNA, thus modulating transfer of information from gene to protein (page 352, 2nd column). Further, it is stated that the present study indicates that JWG2000 is a potent and specific 20-mer phosphorothioate ODN antisense inhibitor of Plk1 expression as its anti-proliferative and antitumor activity in cell culture (A549 and Detroit562) and in mouse models xenografted with A549 cells could be clearly established (page 352, 2nd column).

Driscoll et al. teach a DNA construct encoding an inverted repeat (hairpin) RNA, which is capable of binding to an mRNA sequence of interest and mediating RNA interference in vitro or in vivo (pages 1-5; Figs. 1 and 2). It is taught that the inverted repeat RNAi expression

construct exploits the ability of a vector to generate multiple dsRNA copies, obviating the need for continuous administration of naked dsRNA duplexes, and providing for prolonged the expression of the inhibitory RNA molecules indefinitely *in vivo*. Another advantage of the IR (inverted repeat) constructs is said to be their heritable nature, allowing for the production of transgenic animals and long term, and possibly inducible, silencing of genes (pages 8 and 25). The IR constructs are taught as having utility for the treatment of neoplastic diseases. According to Driscoll et al., the aberrant expression of oncogenes in certain cancers may be targeted for gene silencing using the compositions and methods of the invention (page 9).

Importantly, Driscoll et al. teach that double-stranded RNA is at least an order of magnitude more potent at inducing RNA interference than are preparations of either strand alone (page 1). According to Driscoll et al., the surprising properties of dsRNA-mediated interference prompted users to abandon the term "antisense" and to begin referring to the process as "RNA interference." One of skill in the art may infer from these teaching that dsRNA, such as hairpin RNA, is more potent than antisense or sense strands alone. One of skill in the art would therefore be motivated to make and use the dsRNA expression vectors taught by Driscoll et al. to down regulate a gene of interest since the inverted repeat expression constructs and the transcripts they encode are said to have specific advantages for the down regulation of target genes.

Driscoll et al. teach that the IR expression constructs comprise a promoter element operably linked to a first coding sequence in a sense orientation, which is in turn linked to second coding sequence in an antisense orientation (page 11). The first and second coding sequences may range between 20 and 2500 nucleotides in length (page 11) and may be separated by a spacer sequence of between 300 and 1500 nucleotides in length (page 3). The promoters may be

any of those listed on pages 3 and 12-13. The IR expression construct may also comprise a 3' terminator sequence (page 14). Expression of the IR gene from the promoter results in the formation of a double stranded "snap back" RNA, capable of abrogating the expression of an endogenous gene (page 25 and see Figs.1 and 2). Exemplary vectors are described in Table II and in examples I–III, pages 35–50, and shown in Figs. 4–6.

Additonally, Driscoll et al. teach that IR expression vectors are generally administered to a patient as a pharmaceutical composition (page 30). Accordingly, the pharmaceutical composition may be formulated for administration via direct injection into the brain or intravenous injection (pages 30-31). For direct injection (i.e., bolus injection) into the brain, it is taught that the vector should be dispersed in a medium similar in composition to cerebrospinal fluid (page 31). Alternatively, the vector may be formulated in buffered saline (page 30).

It would have been obvious to one of ordinary skill in the art to use the cDNA sequence disclosed by Holtrich et al. and the baseline antisense studies of Elez et al. to generate short hairpin RNA expression vectors, as taught by Driscoll *et al.,* for inhibition of PLK1 gene expression *in vitro* and *in vivo.*

One would have been motivated to create such compounds because Elez et al. expressly teach that PLK1 could serve as target for anti-cancer therapy antisense compounds and that interfering with PLK1 expression using an antisense oligonucleotide blocks tumor cell proliferation; and because Driscoll et al. teach that dsRNA, such as hairpin RNA generated by an expression construct may be a more potent inhibitor of mRNA expression than either sense or antisense oligos alone.

One would have a reasonable expectation of success given that Driscoll et al. fully describe the materials and methods necessary to generate and use inverted repeat constructs to virtually any known gene such as polo-like kinase, whose sequence is disclosed in the prior art by Holtrich et al. Futhermore, Elez et al. teach that antisense treatment of proliferating cells expressing PLK1 is an effective therapy for reducing tumor size. Given the relative higher potency of dsRNA, as taught by Driscoll et al., one of skill would have been motivated and had a reasonable expectation of success to build and use dsRNA expressing vectors as an additional tool to study and manipulate PLK1 expression in cultured cells and live animals.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

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Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Holtrich et al. (1994); Elez et al. (2000); and Driscoll et al. as applied to claims 6–11, 13, 14, 16–18 above, and further in view of Kennerdell et al. (2000) *Nature Biotechnology* 17:896–898; and Martinek et al. (2000) *Genetics* 156:1717–1725.

Claim 12 recites an RNA expression system according to claim 11 having a spacer sequence of 3 to 10 nucleotides.

Holtrich et al. (1994); Elez et al. (2000); and Driscoll et al. are relied upon for the reasons given above. These references do not teach a IR, hairpin expression construct, wherein the complementary sequences are separated by a spacer sequence of 3 to 10 nucleotides.

Driscoll et al. teach that the inverted repeat gene may comprise a spacer, or linker sequence of between 300 and 1500 nucleotides in length (page 3).

Furthermore, the prior art is replete with teachings of hairpin expression constructs encoding stem-loop RNA (e.g., ribozymes, tRNA, and small RNAs) having various loop and stem sizes.

For example, Kennerdell et al. disclose an RNA expression construct for expressing interfering, hairpin-loop RNA targeted to a *lacZ* transgene in *Drosophila* (page 896-7, Fig. 2) The construct is said to comprise an inverted repeat gene sequence having dyad symmetry centered about a five (5)-base pair linker, expressed from an inducible expression vector (Fig. 1 and 2, legends).

Similarly, Martinek et al. disclose an inverted repeat expression construct for inhibiting endogenous gene expression in *Drosophila*, comprising a 67-nt spacer region (page 1719–20, Fig. 1).

Taken together, the teachings of Driscoll et al., Kennerdell et al., Martinek et al. imply that the loop size, or spacer sequence, separating complementary sense and antisense sequences in an RNA expression construct is a parameter that may vary from construct to construct. Each of the groups teaches effective gene silencing using shRNAs with different loop sizes ranging from 5 to 1500 nucleotides. Kennerdell et al., in particular, teaches that the spacer sequence may be as small as five nucleotides while still providing for the formation of a hairpin RNA and effective gene silencing. Reading these disclosures at the time the instant invention was made, one of skill in the art may have reasonably inferred that the exact size of the spacer sequence chosen for any particular expression construct may vary, ranging anywhere from 5 to 1500 nts,

without adversely affecting the outcome. Accordingly, it may be concluded that it would have been an obvious matter of design choice to make an expression construct with a spacer region of the size claimed in claim 12.

> MPEP 2144.04, subsection VI, C
> *In re Kuhle*, 526 F.2d 553, 188 USPQ
> 7 (CCPA 1975) (the particular placement of a contact in a conductivity measuring device was held to be an obvious matter of design choice). However, "The mere fact that a worker in the art could rearrange the parts of the reference device to meet the terms of the claims on appeal is not by itself sufficient to support a finding of obviousness. The prior art must provide a motivation or reason for the worker in the art, without the benefit of appellant's specification, to make the necessary changes in the reference device." Ex parte Chicago Rawhide Mfg. Co., 223 USPQ 351, 353 (Bd. Pat. App. & Inter. 1984).

In the instant case, one possible motivation to select a spacer sequence of the size recited in claim 12 may be to facilitate cloning. For example, Martinek et al., as part of their study of the use of inverted repeat expression constructs, state that 67 bp gaps were chosen to facilitate cloning (page 1719, 1st column).

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Holtrich et al. (1994); Elez et al. (2000); and Driscoll et al. as applied to claims 6–11, 13, 14, 16–18 above, and further in view of Noonberg et al. (US Patent No. 5,624,803).

Claim 15 recites an RNA expression system according to claim 6, wherein the RNA promoter is U6 or H1.

Holtrich et al. (1994); Elez et al. (2000); and Driscoll et al. are relied upon for the reasons given above. These references do not teach a IR, hairpin expression construct, wherein the RNA promoter is U6 or H1.

Noonberg et al. disclose compositions and methods for generating U6 Pol III-driven expression cassettes for use in delivering antisense, ribozyme, and triplex formining oligonucleotides intracellularly. It is taught that a distinct advantage of U6 Pol III promoters in such expression cassettes is the ability to generate oligos of a predetermined and well-defined length and sequence (column 12, lines 30-65). The Pol III U6 promoter is said to require only upstream sequences for initiation and is said to terminate cleanly upon reaching a string of 4-7 thymidine residues. Accordingly, the U6 Pol III promoter is well suited for generating high yields of short RNA oligos lacking extra, undesirable 5' sequences. The invention is summarized in column 13, lines 5-15. The invention is said to comprise a Pol III promoter such as the U6 promoter, a specific nucleotide sequence, which may designed so as to form a hairpin structure (columns 17-18), and a termination signal.

It would have been obvious to one of ordinary skill in the art to use U6 Pol III driven expression cassettes as taught by Noonberg et al. to generate short hairpin RNA expression vectors, as taught by Driscoll *et al.,* for inhibition of PLK1 gene expression in cells *in vitro* and *in vivo*.

One would have been motivated to create such compounds because Noonberg et al. expressly teach that U6 Pol III promoters are highly suitable for the purpose of expressing short, therapeutic RNA oligos intracellulary, as U6-type promoters terminate cleanly and result in oligos of a well defined sequence and length. In contrast, Pol II promoters are said to transcribe

at lower frequencies, be cell-type specific, and generate transcripts with variable lengths and long polyadenylated tails (columns 17-18).

One would have a reasonable expectation of success given that Noonberg et al. fully describe the materials and methods necessary to generate U6-driven expression cassettes.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on Mon–Fri, 8:00 am–4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval system (PAIR). Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Louis V. Wollenberger, Ph.D.
Examiner
Art Unit 1635

November 29, 2005

SEAN McGARRY
PRIMARY EXAMINER
1635

Notice to Comply	Application No. 10/505,482	Applicant(s) STREBHARDT ET AL.	
	Examiner Louis V. Wollenberger	Art Unit 1635	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Amino acid/nucleic acid sequences set forth in Figs. 13A and 17A, Table I (page 1/1 of the specification), and in pages 59, 65, 68, 69, and 70, do not have SEQ ID NO: identifiers

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

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